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ORIGINAL ARTICLE

Thrombolytic therapy in cardiac arrest caused by cardiac etiologies or presumed pulmonary embolism: An updated systematic review and meta-analysis

Omar A. Alshaya BSc, Pharm, PharmD, BCPS[1,2,3] | Abdulrahman I. Alshaya BSc, Pharm, PharmD, BCPS, BCCCP[1,2,3] | Hisham A. Badreldin BSc, Pharm, PharmD, BCPS, BCCP, FCCP[1,2,3] | Sarah T. Albalawi[1] | Sarah T. Alghonaim[1] | Majed S. Al Yami BSc, Pharm, PharmD, BCPS[1,2,3]

[1]Department of Pharmacy Practice, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[2]Pharmaceutical Care Services, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia

[3]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

Correspondence
Omar A. Alshaya, Department of Pharmacy Practice, College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, PO Box 3660 Riyadh 11481, Saudi Arabia.
Email: omaraalshaya@gmail.com

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Abstract

Background: Many cardiac arrest cases are encountered annually worldwide, with poor survival. The use of systemic thrombolysis during cardiopulmonary resuscitation for the treatment of cardiac arrest remains controversial.

Objectives: Evaluate the safety and efficacy of systemic thrombolysis in patients with cardiac arrest due to presumed or confirmed pulmonary embolism or cardiac etiology.

Methods: We searched the PubMed and Cochrane databases from inception through April 2021 to identify relevant randomized controlled trials and observational studies. The primary efficacy and safety outcomes were survival to hospital discharge and reported bleeding, respectively. Sensitivity analysis was performed on the basis of study design and etiology of cardiac arrest.

Results: Eleven studies were included, with 4696 patients (1178 patients received systemic thrombolysis, and 3518 patients received traditional therapy). There was a higher rate of survival to hospital discharge in patients who received systemic thrombolysis versus no systemic thrombolysis (risk ratio [RR], 1.35; 95% confidence interval [CI], 0.95-1.91). There were also higher rates of survival at 24 hours (RR, 1.24; 95% CI, 0.97-1.59) and hospital admission (RR, 1.53; 95% CI, 1.04-2.24), and return of spontaneous circulation (ROSC) (RR, 1.34; 95% CI, 1.05-1.71) with the use of systemic thrombolysis. Impacts on survival to discharge and survival at 24 hours were not statistically significant. Patients receiving systemic thrombolysis had a 65% increase in bleeding events compared with no systemic thrombolysis (RR, 1.65; 95% CI, 1.20-2.27).

Conclusion: Systemic thrombolysis in cardiac arrest did not improve survival to hospital discharge and led to more bleeding events. However, it increased the rates of hospital admission and ROSC achievement.

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KEYWORDS
cardiac arrest, cardiopulmonary resuscitation, systemic thrombolytic therapy

Essentials

- Blood clots are a cause of cardiac arrest, and can be treated with clot-busting medications (thrombolytics).
- We studied the benefits of these medications in patients with cardiac arrest aged ≥16 years.
- Thrombolytics did not improve survival to hospital discharge and increased bleeding.

1 | INTRODUCTION

In the United States, >350 000 individuals develop cardiac arrest each year, with poor survival rates.[1] The predominant causes of cardiac arrest are pulmonary embolism (PE) and acute myocardial infarction (AMI), both of which can be treated with intravenous thrombolysis. In the United States, survival rates to hospital discharge were only 10.4% for out-of-hospital cardiac arrest (OHCA) and 25.8% for in-hospital cardiac arrest (IHCA). In Europe, survival to hospital discharge was only 8% in OHCA, based on data from 27 countries, and 18.4% in IHCA from one prospective study representing 144 hospitals in the United Kingdom.[2,3]

Evidence on the outcomes of thrombolytic therapy in patients with cardiac arrest has revealed a minimal impact on hospital mortality. In a previous randomized controlled trial (RCT) of patients with cardiac arrest due to cardiac etiologies, there was no observed difference in overall survival with the use of systemic thrombolysis with an increased risk of bleeding.[4] This finding was also supported by a Canadian RCT that compared thrombolytic therapy with placebo in patients with pulseless electrical activity (PEA) and cardiac arrest and showed no beneficial effect of thrombolysis.[5] Thrombolytic agents and their dosing have been heavily debated over the past decade, given their use to treat presumed AMI or PE; however, current guidelines endorse the use of thrombolysis in cardiac arrest secondary to presumed PE with weak recommendations.[6-8]

Most studies that investigated thrombolysis in undifferentiated PEA were suspected but not necessarily confirmed PE.[4,5,9] The most recent meta-analysis by Wang et al[10] evaluated nine studies with a total of 4384 patients with cardiac arrest. They concluded an increased risk of bleeding secondary to systemic thrombolysis administration with no significant improvement in survival to hospital discharge. However, a recent large registry-based analysis from France that included 14 253 patients found better 30-day mortality outcomes in patients with cardiac arrest who received thrombolysis.[11] One major factor that could explain these inconsistent findings is the level of certainty of practitioners' diagnoses of PE or AMI in cardiac arrest cases. The objective of this meta-analysis was to provide an updated evaluation of the safety and efficacy of systemic thrombolysis in patients presenting with cardiac arrest due to presumed or confirmed PE or cardiac etiology.

2 | METHODS

A comprehensive systematic review was conducted using the PubMed and Cochrane databases from inception through April 2021 to identify studies that investigated the safety and efficacy of thrombolysis during cardiac arrest of presumed PE or cardiac etiologies. The search was conducted using medical subject headings and keywords for cardiopulmonary resuscitation (CPR), heart arrest, OHCA, thrombolytic therapy, and tissue plasminogen activator. We also searched the references of the identified studies to identify any other relevant studies for inclusion. The review process adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[12]

Studies were considered eligible for inclusion if thrombolytic therapy was administered during CPR, if the study included adults ≥16 years of age, if data were extracted from original studies published in English, and if the study evaluated at least one of the predetermined primary and secondary outcomes of this study. Studies were excluded if thrombolysis was administered before or after CPR, if data were not compared to a control group, or if data were presented as conference abstracts.

The identified studies of interest were reviewed and assessed against the inclusion criteria by three reviewers (OA, SB, and SG). Data pertaining to the clinical outcomes of interest were extracted and reviewed for quality and accuracy by two authors (OA and AA). The risk of bias for each study was assessed using the Cochrane Collaboration Risk of Bias Assessment Tool 2.0 for RCTs and the Newcastle-Ottawa Scale (NOS) for observational cohort studies.[13,14] The NOS awards up to nine stars for observational cohort studies: four stars for the selection of included patients, two stars for comparability of cohorts based on the design and analysis, and three stars for the assessment of outcomes and adequacy of follow-up. The quality of the included observational cohort studies was determined based on the number of stars obtained: low quality: 0 to 3, medium quality: 4 to 6, and high quality: 7 to 9. Two authors (OA and AA) assessed the quality of included studies. If there was a disagreement, a third experienced author was consulted to reach a consensus. The following data were collected from each study: study authors, publication year, study design, etiology of cardiac arrest, thrombolytic agent used, dose, adjunctive therapy, number of patients in the treatment and control groups, and clinical outcomes of interest. This study was exempted from ethical approval by the insitutional review board at King Abdullah International Medical Research Center.

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2.1 | Study outcomes

The primary efficacy outcome of interest in this meta-analysis was survival to hospital discharge, and the primary safety outcome was reported bleeding. The secondary outcomes were survival at 24 hours, hospital admission (defined as either admission to the emergency department or intensive care unit), return of spontaneous circulation (ROSC), survival at 30 days, and neurological outcomes based on the cerebral performance category (CPC) where CPC 1 indicates good cerebral performance, CPC 2 indicates moderate cerebral disability, CPC 3 indicates severe cerebral disability, CPC 4 indicates coma, and CPC 5 indicates dead or brain dead. An acceptable neurological outcome was considered when patients had a CPC score of 1 or 2. A prespecified subgroup analysis was performed to evaluate the effect of systemic thrombolysis in patients with cardiac arrest caused by presumed PE. Another subgroup analysis was performed to compare the results of the included RCTs only.

2.2 | Statistical analysis

The Mantel-Haenszel random-effects model risk ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated using the metan routine in Stata software version 14.2 (StataCorp, College Station, TX, USA) to estimate the pooled treatment effects of systemic thrombolysis in patients with cardiac arrest. The random-effects model was used as studies looked at different patient population and evaluated different clinical outcomes. Heterogeneity was assessed using I^2 statistics.[13] I^2 values <25 were defined as low, between 25 and 50 as moderate, and >75% as high-level heterogeneity.[13] Publication bias was assessed using funnel plots.

3 | RESULTS

3.1 | Study selection

The literature search yielded 365 potential studies. The majority (n = 354) were irrelevant to the topic or used interventions other than systemic thrombolysis. A large amount of reported literature was either case reports or observational studies with no control arm and were excluded. One study identified from the relevant references of the retrieved studies was a meta-analysis, which was excluded. Eleven studies met our inclusion criteria and were included in this analysis (Figure 1).

3.2 | Study characteristics and quality assessment

Eleven studies with a total of 4696 patients were pooled in the meta-analysis, of which 1178 received systemic thrombolysis and 3518 received traditional therapy. Of the 11 studies, 3 were RCTs, 1 was a post hoc analysis of an RCT, 2 were observational prospective studies, and 5 were observational retrospective studies. All observational studies compared their treatment with that of a control arm. The details of each study, including the systemic thrombolysis regimen used, are summarized in Table 1.[15-21] The quality of the included studies was assessed, and the results are presented in Table 2. Overall, the included RCTs were considered strong evidence with a low risk for bias, and observational studies were deemed moderate to high quality.

3.3 | Summary of the included studies

The role of alteplase during CPR was investigated in patients with OHCA who did not achieve ROSC within 15 minutes due to cardiac reasons.[19] Two patients who received alteplase developed gastric ulcer bleeding and required blood transfusion. ROSC was achieved in 68% of the patients in the treatment group (n = 40) and in 44% of the controls (n = 50; $P = .03$).

Another study included patients who developed OHCA due to nontraumatic etiologies (AMI in 60.2% and PE in 17.6%).[15] ROSC was achieved in 70.4% of the alteplase group (n = 108) compared with 51% of the control group (n = 216; $P = .001$). Bleeding complications from autopsy results showed that six patients in the alteplase group had bleeding and seven in the controls.

In 2002, an RCT was conducted to investigate the role of alteplase in cardiac arrest occurring either outside the hospital or in the emergency department due to unknown or presumed cardiovascular causes.[5] The primary outcome of survival to hospital discharge was achieved in only one patient in the treatment group (n = 117) and no patients in the control group (n = 116; $P = .99$).

Additionally, the bleeding complications were investigated in a retrospective study involving 66 patients (36 patients receiving alteplase and 30 control patients).[16] Major bleeding occurred more frequently with alteplase administration than in the controls (25% vs 10%; $P = .15$).

In 2004, another RCT investigated the role of tenecteplase (50-mg bolus) in patients with OHCA (n = 19) compared with a placebo group (n = 16).[17] ROSC was achieved in 42% and 6% of the treatment and control groups, respectively (95% CI, 11-61).

Similarly, in a study involving 163 patients (50 receiving systemic thrombolysis and 113 controls), tenecteplase was associated with increased ROSC achievement compared with controls (26% vs 12.4%; $P = .04$).[18]

In a post hoc analysis, the effect of alteplase on hospital admission (99 receiving alteplase, 1087 controls) was assessed. More hospital admissions were achieved with alteplase than with controls (45.5% vs 32.7%; $P = .01$).[9]

In 2008, the Thrombolysis in Cardiac Arrest (TROICA) study was conducted in patients with OHCA who were randomly assigned to receive tenecteplase (n = 525) or placebo (n = 525).[4] The 30-day survival rate did not differ between the two groups (14.7% with tenecteplase and 17% with placebo; $P = .36$).

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TABLE 1 Characteristics of included studies in the meta-analysis

Study	Year	Design	Etiology	Thrombolytic agent	Dose	Adjunctive therapy	Number of patients, thrombolysis/ control	Outcomes
Böttiger[19]	2001	Prospective	Cardiac	Alteplase	50-mg bolus (repeat if needed)	Heparin	40/50	• Survival to hospital discharge (RR,1.88; 95% CI, 0.57-6.19) • Survival at 24 h (RR,1.59; 95% CI, 0.81-3.11) • Hospital admission (RR, 1.92; 95% CI, 1.16-3.16) • ROSC (RR, 1.53; 95% CI, 1.05-2.24) • Bleeding (RR, 6.22; 95% CI, 0.31-125.98)
Lederer[15]	2001	Retrospective	Nontraumatic	Alteplase	100 mg (15-mg bolus, followed by 50-mg infusion over 30 min and 35 mg over 60 min)	Heparin +Aspirin	108/216	• Survival to hospital discharge (RR, 1.62; 95% CI, 1.03-2.55) • Survival at 24 h (RR, 1.46; 95% CI: 1.11-1.92) • ROSC (RR, 1.45; 95% CI, 1.21-1.73) • Bleeding (RR, 0.88; 95% CI, 0.32-2.41)
Abu-Laban[5]	2002	RCT	Cardiac	Alteplase	100 mg over 15 min	Heparin, aspirin, or both	117/116	• Survival to hospital discharge (RR, 2.97; 95% CI, 0.12-72.27) • Survival at 24 h (RR, 8.92; 95% CI, 0.49-163.90) • Hospital admission (RR, 1.16; 95% CI, 0.40-3.34) • ROSC (RR, 0.92; 95% CI, 0.57-1.48) • Bleeding (RR, 2.97; 95% CI, 0.31-28.18)
Janata[16]	2003	Retrospective	PE	Alteplase	0.6-1 mg/kg (max, 100 mg)	Heparin	36/30	• Survival to hospital discharge (RR, 2.92; 95% CI, 0.65-13.01) • Survival at 24 h (RR, 2.26; 95% CI, 1.10-4.64) • ROSC (RR, 1.54; 95% CI, 0.96-2.46) • Bleeding (RR, 2.50; 95% CI, 1.14-5.49)
Fatovich[17]	2004	RCT	Cardiac	Tenecteplase	50-mg bolus	Not specified	19/16	• Survival to hospital discharge (RR, 0.84; 95% CI, 0.06-12.42) • Hospital admission (RR, 1.68; 95% CI, 0.17-16.91) • ROSC (RR, 6.74; 95% CI, 0.94-48.29)
Bozeman[18]	2006	Prospective	Cardiac	Tenecteplase	Ranged from 30 to 50 mg (mean, 0.54 mg/kg; range, 0.26–0.77 mg/kg)	Heparin	50/113	• Survival to hospital discharge (RR, 11.18; 95% CI, 0.55-228.64) • Survival at 24 h (RR, 11.18; 95% CI, 0.55-228.64) • Hospital admission (RR, 29.06; 95% CI, 1.67-506.11) • ROSC (RR, 2.10; 95% CI, 1.07-4.13) • Neurological status (RR, 11.18; 95% CI, 0.55-228.64) • Bleeding (RR, 15.65; 95% CI, 0.82-297.38)
Stadlbauer[9]	2006	Post-hoc analysis	Nontraumatic	Tenecteplase or reteplase	Variable – depends on participating center	Heparin	99/1087	• Survival to hospital discharge (RR, 1.49; 95% CI, 0.89-2.51) • Hospital admission (RR, 1.39; 95% CI, 1.10-1.76)

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TABLE 1 (Continued)

Study	Year	Design	Etiology	Thrombolytic agent	Dose	Adjunctive therapy	Number of patients, thrombolysis/control	Outcomes
Böttiger[4]	2008	RCT	Cardiac	Tenecteplase	Weight-based dosing: (<60 kg, 30 mg; 60-69 kg, 35 mg;, 70-79 kg, 40 mg; 80-89 kg, 45 mg; ≥90 kg, 50 mg)	None	525/525	• Survival to hospital discharge (RR, 0.86; 95% CI, 0.65-1.14) • 30-day survival (RR, 0.87; 95% CI: 0.65-1.14) • Survival at 24 h (RR, 0.92; 95% CI, 0.77–1.10) • Hospital admission (RR, 0.97; 95% CI, 0.87-1.09) • ROSC (RR, 1.01; 95% CI, 0.90-1.12) • Neurological status (RR, 1.12; 95% CI, 0.88-1.42) • Bleeding (RR, 1.53; 95% CI, 1.02-2.30)
Renard[20]	2011	Retrospective	Nontraumatic	Alteplase or tenecteplase	Alteplase: 50-mg bolus Tenecteplase: 100-UI/kg bolus	Not specified	107/1154	• Hospital admission (RR, 2.02; 95% CI, 1.62-2.53)
Yousuf[21]	2016	Retrospective	PE	Alteplase	100 mg	Not specified	19/23	• Survival to hospital discharge (RR, 1.21; 95% CI, 0.19-7.80) • Survival at 24 h (RR, 0.99; 95% CI, 0.52-1.87) • Bleeding (RR, 3.63; 95% CI, 0.41-32.13)
Javaudin[11]	2019	Retrospective	PE	Alteplase, tenecteplase, or streptokinase	Alteplase: median dose of 50 mg (50-80 mg) Tenecteplase: median dose of 45 mg (35-50 mg) Streptokinase: dose unknown	Not specified	58/188	• Survival at 24 h (RR, 1.04; 95% CI, 0.84-1.30) • 30-day survival (RR, 2.43; 95% CI, 1.08-3.67) • Neurological status (RR, 2.16; 95% CI, 0.80-5.82) • Bleeding (RR, 1.08; 95% CI, 0.30-3.86)

Abbreviations: CI, confidence interval; PE, pulmonary embolism; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio.

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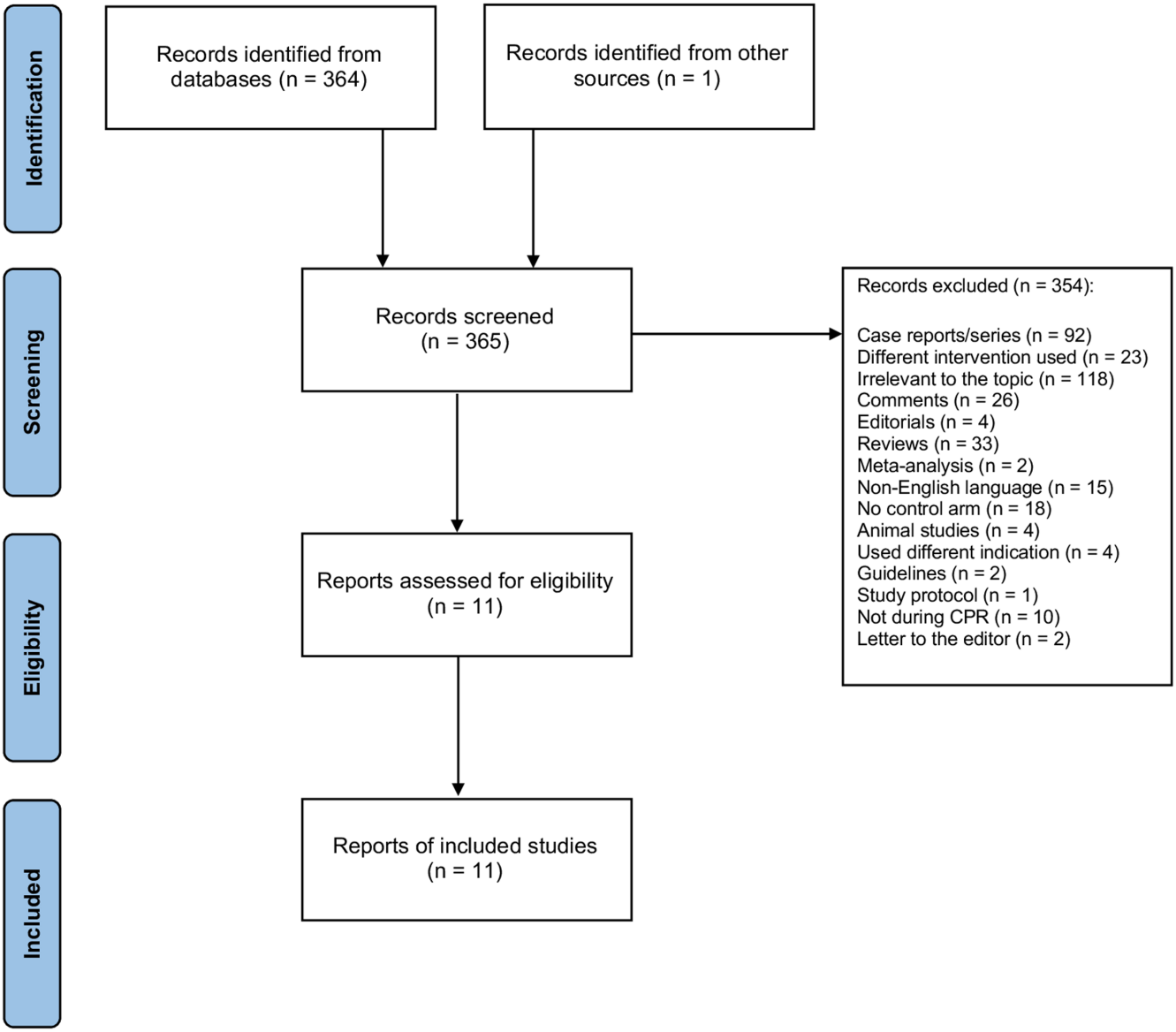
Identification
Records identified from databases (n = 364)
Records identified from other sources (n = 1)
Screening
Records screened (n = 365)
Records excluded (n = 354):
Case reports/series (n = 92)
Different intervention used (n = 23)
Irrelevant to the topic (n = 118)
Comments (n = 26)
Editorials (n = 4)
Reviews (n = 33)
Meta-analysis (n = 2)
Non-English language (n = 15)
No control arm (n = 18)
Animal studies (n = 4)
Used different indication (n = 4)
Guidelines (n = 2)
Study protocol (n = 1)
Not during CPR (n = 10)
Letter to the editor (n = 2)
Eligibility
Reports assessed for eligibility (n = 11)
Included
Reports of included studies (n = 11)

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of study selection, included and excluded studies. CPR, cardiopulmonary resuscitation

After the TROICA study, Renard et al[20] evaluated the effect of systemic thrombolysis (alteplase 50-mg intravenous [IV] bolus or tenecteplase 100 UI/kg IV bolus) (n = 107) compared with controls (n = 1154) on survival to hospital admission. A higher number of patients achieved the primary outcome with treatment compared with controls (47.7% vs 23.6%; $P < .001$).

In 2016, a single-center retrospective study of alteplase in cardiac arrest due to presumed PE found that patients who received 100 mg IV alteplase (n = 19) were not statistically different from the controls (n = 23) in terms of survival to hospital discharge (10.5% vs 8.7%; $P = 1.00$).[21]

Recently, Javaudin et al[11] investigated the benefit of systemic thrombolysis in OHCA due to a diagnosis of PE confirmed on hospital admission in a large retrospective multicenter study in France. The systemic thrombolysis group (n = 58) achieved a higher 30-day survival rate than the control group (n = 188) (16% vs 6%; $P = .005$).

3.4 | Primary outcomes

3.4.1 | Survival to hospital discharge

Nine studies were pooled to compare this outcome with a total of 3148 patients, of which 1005 patients received systemic thrombolysis and 2143 patients were in the control group. Higher rates of survival to hospital discharge across all study designs were observed in patients who received systemic thrombolysis than in those who did not receive systemic thrombolysis, but the difference was not statistically significant (RR, 1.35; 95% CI, 0.95-1.91), with moderate-level heterogeneity (I^2= 33.6%; $P = .15$; Figure 2A). These results were different based on RCTs only data, as the rates of survival to hospital discharge were lower by 13% in patients who received systemic thrombolysis compared with those who did not receive systemic thrombolysis. In a subgroup analysis based on the cause of cardiac arrest, survival to

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TABLE 2 Quality assessment of included studies

Newcastle-Ottawa Scale for assessing the quality of included cohort studies								
Study	**Böttiger, 2001[19]**	**Lederer, 2001[15]**	**Janata, 2003[16]**	**Bozeman, 2006[18]**	**Stadlbauer, 2006[9]**	**Renard, 2011[20]**	**Yousuf, 2016[21]**	**Javaudin, 2019[11]**
Selection								
Representativeness of exposed cohort	–	–	*	*	*	–	*	*
Selection of nonexposed cohort	–	–	–	–	–	*	–	*
Ascertainment of exposure	*	–	–	*	*	–	*	–
Demonstration that outcome of interest was not present at start of study	*	*	*	*	*	*	*	*
Comparability on basis of design and analysis	*	*	–	–	*	*	*	*
Outcome								
Assessment of outcome	*	*	–	*	*	*	*	*
Follow-up long enough	–	–	*	–	–	–	–	*
Adequacy of follow-up	*	–	–	–	*	–	–	–
Total stars	5	3	3	4	6	4	5	7

The Cochrane Risk of Bias tool for assessing the quality of included RCTs			
Study	**Abu-Laban, 2002[5]**	**Fatovich, 2004[17]**	**Böttiger, 2008[4]**
Random assignment	Low risk	Low risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk
Blinding of participants	Low risk	Low risk	Low risk
Blind evaluation for outcomes	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk

Abbreviation: RCTs, randomized controlled trials.

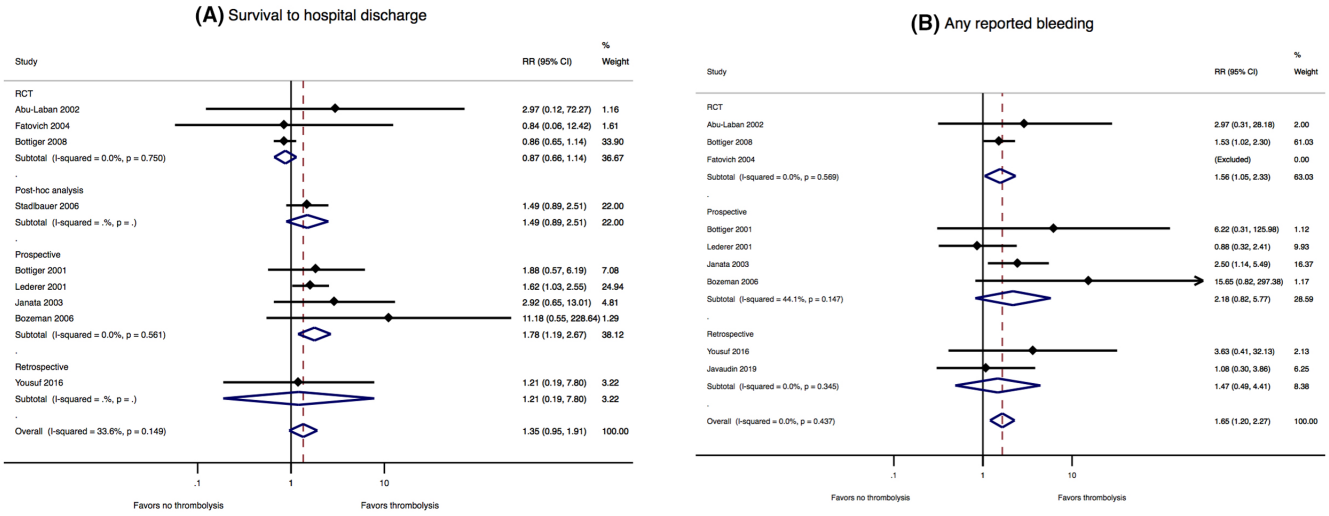
(A) Survival to hospital discharge
Study
RR (95% CI)
% Weight
RCT
Abu-Laban 2002 2.97 (0.12, 72.27) 1.16
Fatovich 2004 0.84 (0.06, 12.42) 1.61
Bottiger 2008 0.86 (0.65, 1.14) 33.90
Subtotal (I-squared = 0.0%, p = 0.750) 0.87 (0.66, 1.14) 36.67
Post-hoc analysis
Stadlbauer 2006 1.49 (0.89, 2.51) 22.00
Subtotal (I-squared = .%, p = .) 1.49 (0.89, 2.51) 22.00
Prospective
Bottiger 2001 1.88 (0.57, 6.19) 7.08
Lederer 2001 1.62 (1.03, 2.55) 24.94
Janata 2003 2.92 (0.65, 13.01) 4.81
Bozeman 2006 11.18 (0.55, 228.64) 1.29
Subtotal (I-squared = 0.0%, p = 0.561) 1.78 (1.19, 2.67) 38.12
Retrospective
Yousuf 2016 1.21 (0.19, 7.80) 3.22
Subtotal (I-squared = .%, p = .) 1.21 (0.19, 7.80) 3.22
Overall (I-squared = 33.6%, p = 0.149) 1.35 (0.95, 1.91) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis
(B) Any reported bleeding
Study
RR (95% CI)
% Weight
RCT
Abu-Laban 2002 2.97 (0.31, 28.18) 2.00
Bottiger 2008 1.53 (1.02, 2.30) 61.03
Fatovich 2004 (Excluded) 0.00
Subtotal (I-squared = 0.0%, p = 0.569) 1.56 (1.05, 2.33) 63.03
Prospective
Bottiger 2001 6.22 (0.31, 125.98) 1.12
Lederer 2001 0.88 (0.32, 2.41) 9.93
Janata 2003 2.50 (1.14, 5.49) 16.37
Bozeman 2006 15.65 (0.82, 297.38) 1.17
Subtotal (I-squared = 44.1%, p = 0.147) 2.18 (0.82, 5.77) 28.59
Retrospective
Yousuf 2016 3.63 (0.41, 32.13) 2.13
Javaudin 2019 1.08 (0.30, 3.86) 6.25
Subtotal (I-squared = 0.0%, p = 0.345) 1.47 (0.49, 4.41) 8.38
Overall (I-squared = 0.0%, p = 0.437) 1.65 (1.20, 2.27) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis

FIGURE 2 Rates of primary outcomes between cardiac arrest patients who received thrombolysis versus no thrombolysis during CPR across all study designs. (A) Rates of survival to hospital discharge; (B) rates of any reported bleeding. CI, confidence interval; CPR, cardiopulmonary resuscitation; RCT, randomized controlled trial; RR, risk ratio

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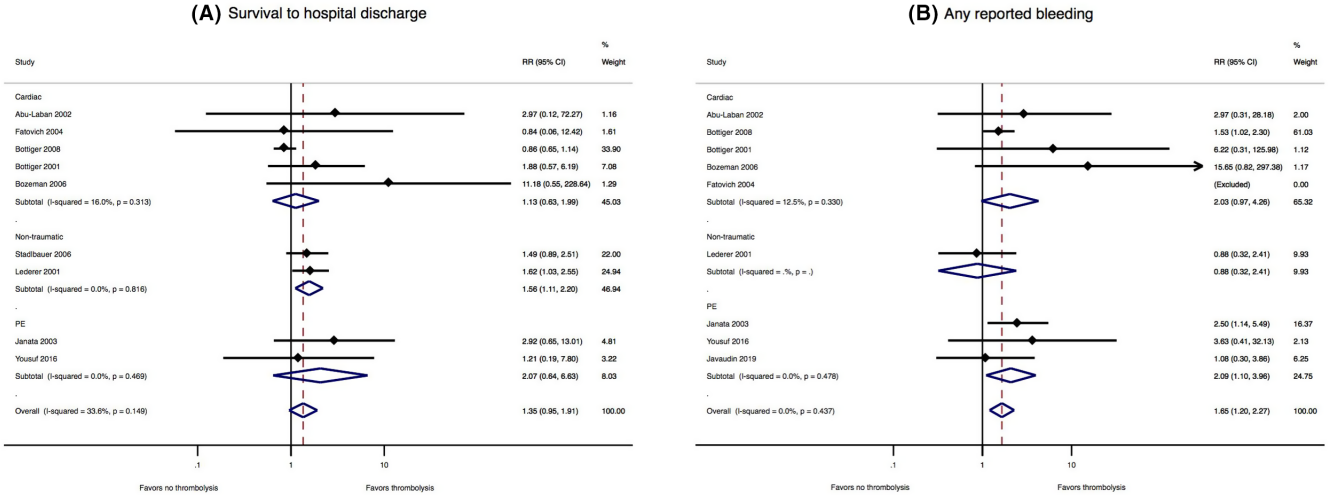
(A) Survival to hospital discharge
Study
RR (95% CI)
% Weight
Cardiac
Abu-Laban 2002 2.97 (0.12, 72.27) 1.16
Fatovich 2004 0.84 (0.06, 12.42) 1.61
Bottiger 2008 0.86 (0.65, 1.14) 33.90
Bottiger 2001 1.88 (0.57, 6.19) 7.08
Bozeman 2006 11.18 (0.55, 228.64) 1.29
Subtotal (I-squared = 16.0%, p = 0.313) 1.13 (0.63, 1.99) 45.03
Non-traumatic
Stadlbauer 2006 1.49 (0.89, 2.51) 22.00
Lederer 2001 1.62 (1.03, 2.55) 24.94
Subtotal (I-squared = 0.0%, p = 0.816) 1.56 (1.11, 2.20) 46.94
PE
Janata 2003 2.92 (0.65, 13.01) 4.81
Yousuf 2016 1.21 (0.19, 7.80) 3.22
Subtotal (I-squared = 0.0%, p = 0.469) 2.07 (0.64, 6.63) 8.03
Overall (I-squared = 33.6%, p = 0.149) 1.35 (0.95, 1.91) 100.00
.1
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Favors no thrombolysis
Favors thrombolysis
(B) Any reported bleeding
Study
RR (95% CI)
% Weight
Cardiac
Abu-Laban 2002 2.97 (0.31, 28.18) 2.00
Bottiger 2008 1.53 (1.02, 2.30) 61.03
Bottiger 2001 6.22 (0.31, 125.98) 1.12
Bozeman 2006 15.65 (0.82, 297.38) 1.17
Fatovich 2004 (Excluded) 0.00
Subtotal (I-squared = 12.5%, p = 0.330) 2.03 (0.97, 4.26) 65.32
Non-traumatic
Lederer 2001 0.88 (0.32, 2.41) 9.93
Subtotal (I-squared = .%, p = .) 0.88 (0.32, 2.41) 9.93
PE
Janata 2003 2.50 (1.14, 5.49) 16.37
Yousuf 2016 3.63 (0.41, 32.13) 2.13
Javaudin 2019 1.08 (0.30, 3.86) 6.25
Subtotal (I-squared = 0.0%, p = 0.478) 2.09 (1.10, 3.96) 24.75
Overall (I-squared = 0.0%, p = 0.437) 1.65 (1.20, 2.27) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis

FIGURE 3 Rates of primary outcomes between patients with cardiac arrest who received thrombolysis versus no thrombolysis during CPR across all causes of cardiac arrest. (A) Rates of survival to hospital discharge; (B) rates of any reported bleeding. CI, confidence interval; CPR, cardiopulmonary resuscitation; RCT, randomized controlled trial; RR, risk ratio

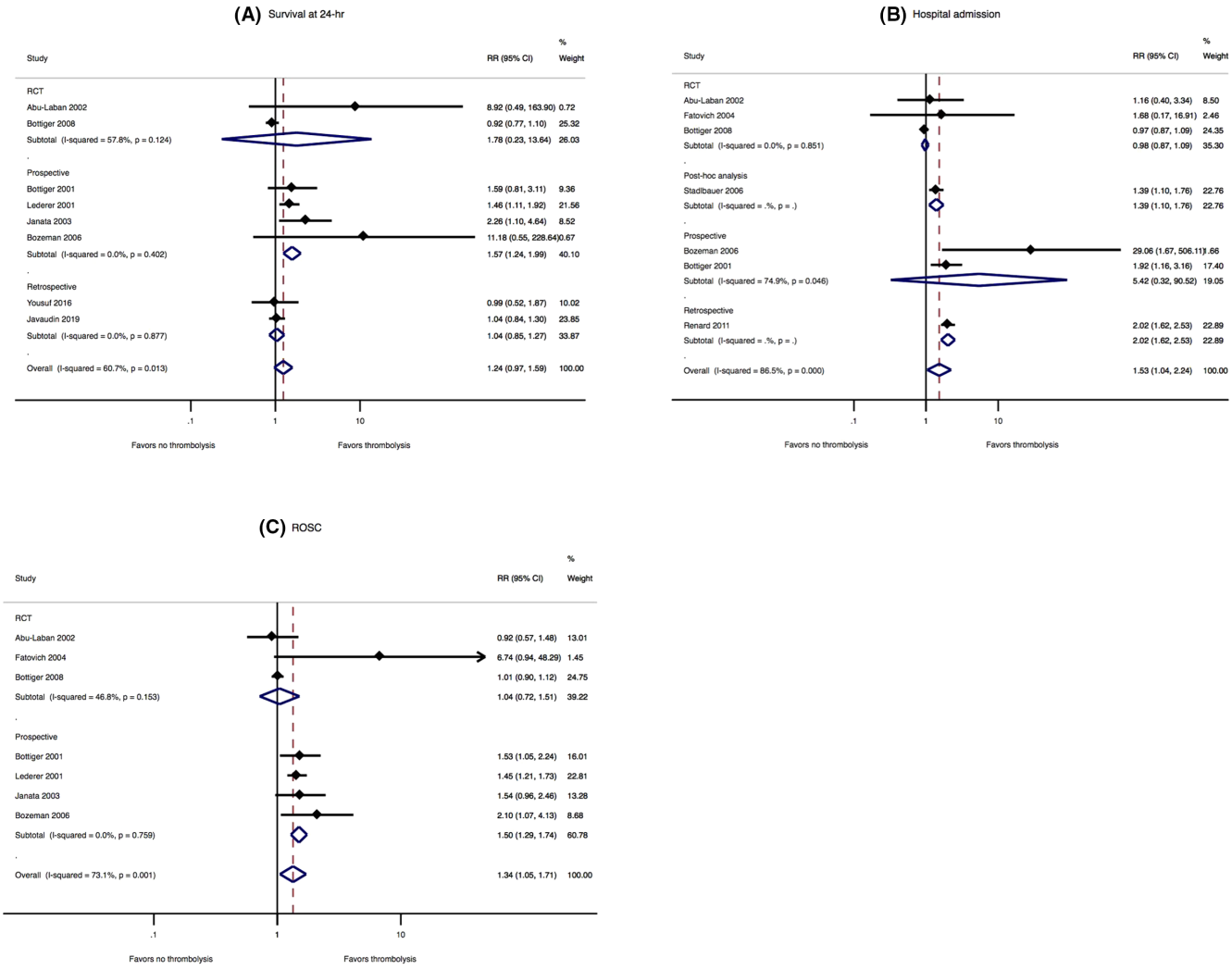
(A) Survival at 24-hr
Study
RR (95% CI)
% Weight
RCT
Abu-Laban 2002 8.92 (0.49, 163.90) 0.72
Bottiger 2008 0.92 (0.77, 1.10) 25.32
Subtotal (I-squared = 57.8%, p = 0.124) 1.78 (0.23, 13.64) 26.03
Prospective
Bottiger 2001 1.59 (0.81, 3.11) 9.36
Lederer 2001 1.46 (1.11, 1.92) 21.56
Janata 2003 2.26 (1.10, 4.64) 8.52
Bozeman 2006 11.18 (0.55, 228.64) 0.67
Subtotal (I-squared = 0.0%, p = 0.402) 1.57 (1.24, 1.99) 40.10
Retrospective
Yousuf 2016 0.99 (0.52, 1.87) 10.02
Javaudin 2019 1.04 (0.84, 1.30) 23.85
Subtotal (I-squared = 0.0%, p = 0.877) 1.04 (0.85, 1.27) 33.87
Overall (I-squared = 60.7%, p = 0.013) 1.24 (0.97, 1.59) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis
(B) Hospital admission
Study
RR (95% CI)
% Weight
RCT
Abu-Laban 2002 1.16 (0.40, 3.34) 8.50
Fatovich 2004 1.68 (0.17, 16.91) 2.46
Bottiger 2008 0.97 (0.87, 1.09) 24.35
Subtotal (I-squared = 0.0%, p = 0.851) 0.98 (0.87, 1.09) 35.30
Post-hoc analysis
Stadlbauer 2006 1.39 (1.10, 1.76) 22.76
Subtotal (I-squared = .%, p = .) 1.39 (1.10, 1.76) 22.76
Prospective
Bozeman 2006 29.06 (1.67, 506.11) 1.66
Bottiger 2001 1.92 (1.16, 3.16) 17.40
Subtotal (I-squared = 74.9%, p = 0.046) 5.42 (0.32, 90.52) 19.05
Retrospective
Renard 2011 2.02 (1.62, 2.53) 22.89
Subtotal (I-squared = .%, p = .) 2.02 (1.62, 2.53) 22.89
Overall (I-squared = 86.5%, p = 0.000) 1.53 (1.04, 2.24) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis
(C) ROSC
Study
RR (95% CI)
% Weight
RCT
Abu-Laban 2002 0.92 (0.57, 1.48) 13.01
Fatovich 2004 6.74 (0.94, 48.29) 1.45
Bottiger 2008 1.01 (0.90, 1.12) 24.75
Subtotal (I-squared = 46.8%, p = 0.153) 1.04 (0.72, 1.51) 39.22
Prospective
Bottiger 2001 1.53 (1.05, 2.24) 16.01
Lederer 2001 1.45 (1.21, 1.73) 22.81
Janata 2003 1.54 (0.96, 2.46) 13.28
Bozeman 2006 2.10 (1.07, 4.13) 8.68
Subtotal (I-squared = 0.0%, p = 0.759) 1.50 (1.29, 1.74) 60.78
Overall (I-squared = 73.1%, p = 0.001) 1.34 (1.05, 1.71) 100.00
.1
1
10
Favors no thrombolysis
Favors thrombolysis

FIGURE 4 Rates of secondary outcomes between cardiac arrest patients who received thrombolysis versus no thrombolysis during CPR across all study designs. (A) Rates of survival at 24 h; (B) rates of hospital admission; (C) rates of ROSC. CI, confidence interval; CPR, cardiopulmonary resuscitation; RCT, randomized controlled trial; ROSC, return of spontaneous circulation; RR, risk ratio

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hospital discharge was significantly higher in patients with nontraumatic causes who received systemic thrombolysis than in those who did not (RR, 1.56; 95% CI, 1.11-2.20) (Figure 3A).

3.4.2 | Reported bleeding

Nine of the included studies reported data on bleeding after systemic thrombolysis. There were a total of 1998 patients, in which 902 patients received systemic thrombolysis and 1096 patients received traditional therapy. The use of systemic thrombolysis across all study designs was associated with a significant incremental risk in reported bleeding events as compared with no systemic thrombolysis (RR, 1.65; 95% CI, 1.20-2.27) with low-level heterogeneity ($I^2 = 0.0\%$; $P = .44$; Figure 2B). These results were more driven by data from RCTs that showed significantly higher incidence of bleeding in patients who received systemic thrombolysis versus those who did not receive systemic thrombolysis (RR, 1.56; 95% CI, 1.05-2.33). In a subgroup analysis based on the cause of cardiac arrest, any reported bleeding was significantly higher in patients with PE who received systemic thrombolysis than in those who did not (RR, 2.09; 95% CI, 1.10-3.96; Figure 3B).

3.5 | Secondary outcomes

3.5.1 | Survival at 24 hours

This outcome was evaluated in eight studies. A total of 2195 patients were included in our analysis, of which 945 patients received systemic thrombolysis and 1250 were in the control group. There was a trend favoring higher rates of survival at 24 hours in patients who received systemic thrombolysis compared with those who did not receive systemic thrombolysis (RR, 1.24; 95% CI, 0.97-1.59), with moderate to high-level heterogeneity ($I^2 = 60.7\%$; $P = .01$; Figure 4A). These results were also consistent on the basis of data from RCTs that showed a 78% increase in the rates of survival at 24 hours in patients who received systemic thrombolysis as compared to no systemic thrombolysis (RR, 1.78; 95% CI, 0.23-13.64).

3.5.2 | Hospital admission

This outcome was assessed in seven of the included studies with a total of 4018 patients. The number of patients who received systemic thrombolysis was 957, and the number of patients in the control group was 3061. Significantly higher rates of hospital admission were observed in patients who received systemic thrombolysis than those who did not (RR, 1.53; 95% CI, 1.04-2.24) with high-level heterogeneity ($I^2 = 86.5\%$; $P = <.001$; Figure 4B). However, data from RCTs did not show significant benefit regarding hospital admission among the group that received systemic thrombolysis versus no systemic thrombolysis (RR, 0.98; 95% CI, 0.87-1.09).

3.5.3 | Return of spontaneous circulation

Seven of the included studies examined the achievement of ROSC with systemic thrombolysis compared with the controls in a total of 1947 patients. Systemic thrombolysis and traditional therapy were administered in 885 and 1062 patients, respectively. Significantly higher rates of ROSC were observed with the use of systemic thrombolysis than with no systemic thrombolysis (RR, 1.34; 95% CI, 1.05-1.71) with moderate- to high-level heterogeneity ($I^2 = 73.1\%$; $P = .001$; Figure 4C). The results from the RCTs did not show a significant difference in ROSC achievement among patients who received systemic thrombolysis as compared with those who did not receive systemic thrombolysis (RR, 1.04; 95% CI, 0.72-1.51).

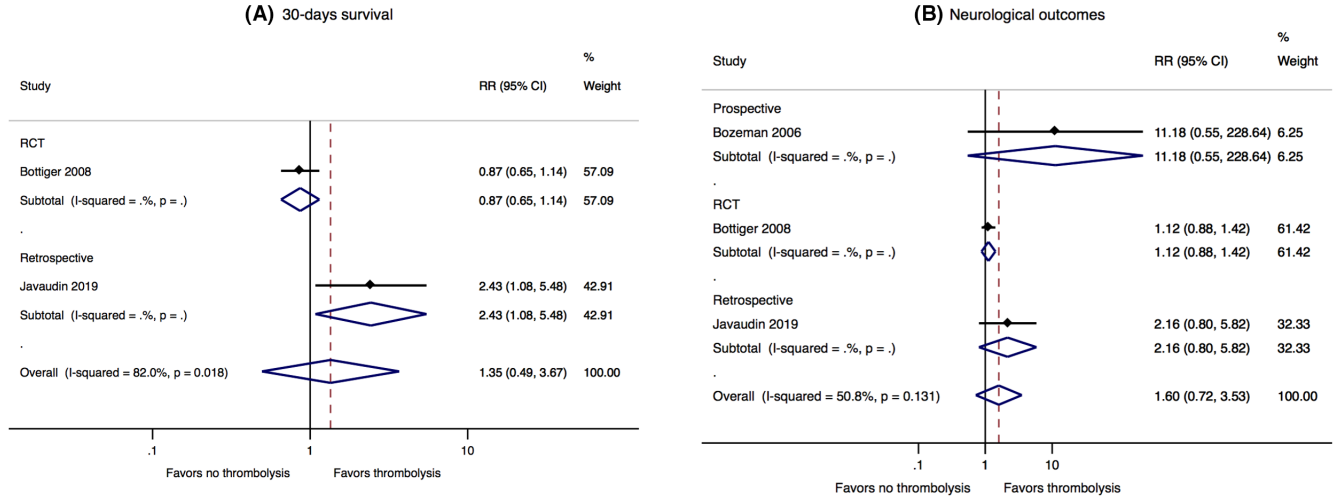

FIGURE 5 Rates of secondary outcomes between patients with cardiac arrest who received thrombolysis versus no thrombolysis during CPR across all study designs. (A) Rates of survival at 30 days; (B) rates of neurological outcomes. CI, confidence interval; CPR, cardiopulmonary resuscitation; RCT, randomized controlled trial; RR, risk ratio

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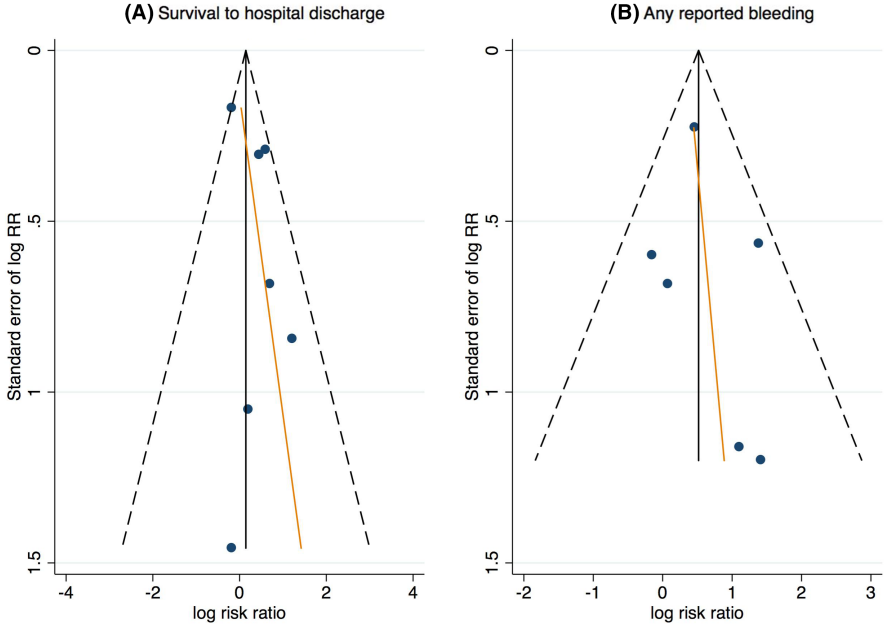

FIGURE 6 Funnel plot for publication bias for primary outcomes. (A) Survival to hospital discharge; (B) any reported bleeding. RR, risk ratio

3.5.4 | Survival at 30 days

This outcome was assessed in only 2 of the 11 included studies with a total of 1296 patients. Systemic thrombolysis and traditional therapy were administered in 538 and 713 patients, respectively. Higher rates of survival at day 30 were observed among patients who received systemic thrombolysis versus those who did not (RR, 1.35; 95% CI, 0.49-3.67) with high-level heterogeneity (I^2 = 82%; P = .02; Figure 5A).

3.5.5 | Neurological outcomes

This important outcome was assessed in only 3 of the 11 included studies with a total of 591 patients. Systemic thrombolysis and traditional therapy were administered to 194 and 397 patients, respectively. The use of systemic thrombolysis resulted in higher rates of achieving acceptable neurological outcomes than no systemic thrombolysis (RR, 1.60; 95% CI, 0.72-3.53) with moderate-level heterogeneity (I^2 = 50.8%; P = .13; Figure 5B).

3.5.6 | Publication bias

No publication bias was identified as shown in the funnel plots for primary outcomes (Figure 6).

4 | DISCUSSION

The results of this updated systematic review and meta-analysis showed that patients who received thrombolytic therapy following cardiac arrest due to presumed pulmonary embolism or cardiac causes had higher rates of survival to hospital discharge, survival at 24 hours, and survival at 30 days than those who did not receive systemic thrombolysis; however, these results were not statistically significant. On the other hand, the use of thrombolytic therapy in this subset of patients was associated with a higher risk of reported bleeding. This significant increase in the risk of bleeding was consistent among RCTs. Achieving higher rates of ROSC and attaining higher rates of hospital admission were the main observed benefits of thrombolytic therapy; however, these results were mainly driven by observational studies. In patients with confirmed PE-related cardiac arrest, thrombolytic therapy was associated with a twofold increase in the risk of bleeding.

Over the years, and because of the experience gained in this field, it has been proposed that thrombolytic therapy during CPR may help stabilize hemodynamics. The suggested theory of the potential benefit of thrombolytic therapy in these patients emerged from experimental studies that showed that thrombolytic therapy during cardiac arrest might enhance microcirculatory reperfusion. These findings indicate that during reperfusion after cardiac arrest, blood coagulation is markedly activated without sufficient endogenous fibrinolysis. Thrombolytic therapy may be indicated because of the extensive coagulation activation and subsequent fibrin formation responsible for inducing microcirculatory reperfusion disorders.[22]

This meta-analysis differed from that previously published by Wang et al.[10] We added two large studies that have recently been published in this field to the literature. In this regard, the meta-analysis by Wang et al did not show any significant improvement in hospital discharge, ROSC, or 24-hour survival rates. In contrast, our meta-analysis showed a beneficial effect of thrombolytic therapy in achieving higher ROSC rates and hospital admissions. This may have contributed to enhanced microcirculation. However, earlier achievement of ROSC did not affect the mortality rate. Previous evidence suggests that close to 70% of individuals who achieve ROSC ultimately die from several

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complications such as post–cardiac arrest syndrome.[23,24] However, we believe that early achievement of ROSC could provide more time to explore further advanced treatment modalities such as but not limited to mechanical circulatory support systems.[25,26]

Similar to Wang et al,[10] and owing to the inconsistent definition of bleeding events among the included studies, we did not evaluate the bleeding outcome based on the bleeding event category. Our findings are also in line with those of Wang et al, who reported that the use of systemic thrombolysis was associated with a significantly increased risk of any reported bleeding. Our analysis did not show any improvement in neurological outcomes in the patients who received systemic thrombolysis.

Our study had several limitations that need to be highlighted. First, our analysis included a small number of RCTs. In addition, there were inconsistencies among the included studies in terms of reported outcomes. Furthermore, the patient population included both patients with PE and patients without PE, which we attempted to minimize by evaluating PE-related studies in a subgroup analysis. Moreover, when we performed the analysis mainly on the included RCTs, there were no differences in the clinical outcomes of interest, except for the increased risk of bleeding in patients who received systemic thrombolysis. We believe that large and well-designed RCTs are warranted to ascertain the relationship between thrombolytic therapy and potential benefits among patients with cardiac arrest. Second, the included studies carried many confounders that are extremely difficult to control, which might affect the net benefit of thrombolytic therapy, such as the definitive diagnosis, dose and duration of thrombolytic therapy, and other supportive and adjunctive therapies. Finally, indication bias for analyses involving observational data could have affected the overall results of the clinical outcomes of interest.

5 | CONCLUSION

In this updated systematic review and meta-analysis, the use of systemic thrombolysis was not associated with an increase in survival to hospital discharge; however, it did lead to an increase in hospital admission, ROSC achievement, and more bleeding events. Rigorous and high-quality RCTs are required to confirm these findings.

AUTHOR CONTRIBUTIONS

All authors participated equally in generating the research idea, conducting the search strategy, reviewing the collected studies for inclusion or exclusion, performing the analysis, writing the manuscript, and reviewing it for the completeness of information.

RELATIONSHIP DISCLOSURE

The authors have no conflicts of interest to declare.

ORCID

Omar A. Alshaya https://orcid.org/0000-0002-2244-0491

TWITTER

Omar A. Alshaya @omaraalshaya
Abdulrahman I. Alshaya @_aalshaya
Hisham A. Badreldin @87HISHAM
Sarah T. Albalawi @saralbl
Sarah T. Alghonaim @SaraAlghonaim
Majed S. Al Yami @MajedSalehAlYa1

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